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# Results of a Prospective Randomized Trial Evaluating Surgery *Versus* Thrombolysis for Ischemia of the Lower Extremity

## The STILE Trial

The STILE Investigators (Appendix A)

### Purpose

This study was designed to evaluate intra-arterial thrombolytic therapy as part of a treatment strategy for patients requiring revascularization for lower limb ischemia caused by nonembolic arterial and graft occlusion.

### Materials and Methods

Patients with native arterial or bypass graft occlusion were randomized prospectively to either optimal surgical procedure or intra-arterial, catheter-directed thrombolysis with recombinant tissue plasminogen activator (rt-PA) or urokinase (UK). Thrombolysis patients required successful catheter placement into the occlusion before infusion of either rt-PA at 0.05 mg/kg/hr for up to 12 hours or UK of 250,000 units bolus followed by 4000 units/min × 4 hours, then 2000 units/min for up to 36 hours. A composite clinical outcome of death, ongoing/recurrent ischemia, major amputation, and major morbidity was the primary endpoint. Additional endpoints were reduction in surgical procedure, clinical outcome classification, length of hospitalization, and outcome by duration of ischemia.

### Results

Randomization was terminated at 393 patients because a significant primary endpoint occurred by the first interim analysis. Failure of catheter placement occurred in 28% of patients who were randomized to lysis, and thus, were considered treatment failures. Thirty-day outcomes demonstrated significant benefit to surgical therapy compared with thrombolysis ($p < 0.001$), primarily because of a reduction in ongoing/recurrent ischemia ($p < 0.001$). However, clinical outcome classification at 30 days was similar. Stratification by duration of ischemia indicated that patients with ischemic deterioration of 0 to 14 days had lower amputation rates with thrombolysis ($p = 0.052$) and shorter hospital stays ($p < 0.04$). Patients with ischemic deterioration of > 14 days who who were were treated surgically had less ongoing/recurrent ischemia ($p < 0.001$) and trends toward lower morbidity ($p = 0.1$). At 6-month follow-up, there was improved amputation-free survival in acutely ischemic patients treated with thrombolysis ($p = 0.01$); however, chronically ischemic patients who were treated surgically had significantly lower major amputations rates ($p = 0.01$). More than half of thrombolysis patients (55.8%) had a reduction in magnitude of their surgical procedure ($p < 0.001$). There was no difference in efficacy or safety between rt-PA and UK; however, in the thrombolysis group as a whole, fibrinogen depletion predicted hemorrhagic complications ($p < 0.01$).

**Conclusions**

Surgical revascularization of patients with < 6 months of ischemia is more effective and safer than catheter-directed thrombolysis. Although ongoing/recurrent ischemia is greater in the patients undergoing thrombolysis, 30-day clinical outcomes are similar, probably because of cross-over treatment to surgery. There is no difference in efficacy or safety between rt-PA and UK, although bleeding occurs in patients with greater fibrinogen depletion. A significant reduction in planned surgical procedure is observed after thrombolysis. Patients with acute ischemia (0–14 days) who were treated with thrombolysis had improved amputation-free survival and shorter hospital stays. However, for patients with chronic ischemia (> 14 days), surgical revascularization was more effective and safer than thrombolysis. Combining a treatment strategy of catheter-directed thrombolysis for acute limb ischemia with surgical revascularization for chronic limb ischemia offers the best overall results.

Catheter-directed thrombolysis is based on the principle that activation of fibrin-bound plasminogen to the active enzyme plasmin is the most effective means of lysing pathologic thrombi.[1] Direct delivery of a thrombolytic agent produces increased plasmin activity at the desired location, protects intrathrombus plasmin from circulating antiplasmins, and permits effective thrombolysis at a reduced dose. The intrathrombus delivery of plasminogen activators has enjoyed greater success than systemic lytic therapy for arterial and graft occlusions.[2–11]

Catheter-directed thrombolysis has been embraced by interventionalists and vascular surgeons. Although some centers have focused on its use for acute arterial and graft thrombosis,[2,4–8] others have extended its use to arterial emboli[11,12] and chronic arterial occlusive disease.[13,14]

Unfortunately, success rates have varied to the degree that intra-arterial thrombolytic therapy has been questioned as a reasonable treatment alternative[15,16] and criticized as not being cost effective.[17] A prospective, randomized study designed to assess the effectiveness of catheter-directed thrombolysis compared with standard surgical intervention for patients with arterial and bypass graft occlusion has not been reported previously.

The STILE study (Surgery *versus* Thrombolysis for Ischemia of the Lower Extremity) was designed to evaluate intra-arterial thrombolytic therapy as part of a treatment strategy for patients who require revascularization for lower limb ischemia caused by nonembolic arterial and graft occlusion.

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## HYPOTHESIS

The primary hypothesis tested by this trial is that there is a difference between thrombolysis and surgery in the rate of occurrence of a composite clinical outcome in patients treated for nonembolic arterial and graft occlusion.

## ADDITIONAL SECONDARY HYPOTHESES

Additional secondary hypotheses include:

1. There is a difference between thrombolysis and surgery in the classification of clinical outcome;
2. Patients who undergo thrombolysis have a reduction in number and magnitude of required surgical revascularization procedures;
3. There is a difference among the treatment groups (surgery, recombinant tissue plasminogen activator [rt-PA] and urokinase [UK]) with respect to composite clinical outcome and its individual components;
4. There is a difference between the treatment groups with respect to combined mortality and amputation;
5. There is a difference in patency rates between rt-PA and UK at 4 and 8 hours, but no difference at the end of study drug infusion;
6. There is no difference in safety between rt-PA and UK.

## MATERIALS AND METHODS

### Patient Population

Patients from 18 to 90 years of age who had signs or symptoms of worsening limb ischemia within the past 6 months who required intervention and those those who had angiographically documented nonembolic arterial or bypass graft occlusion were considered candidates for this trial. The protocol was reviewed and approved by the institutional review board of each participating cen-

**Table 1. EXCLUSION CRITERIA FOR THE STILE TRIAL**

| |
|---|
| Absolute |
| Patients with infected peripheral arterial bypass graft occlusions |
| Patients previously enrolled in this trial |
| Patients with acute embolic occlusion |
| Active, internal bleeding |
| History of any cerebrovascular accident or any intracranial bleeding |
| History of any transient ischemic attack (unless post-TIA CT scan normal) |
| Recent (within 2 mos) intracranial or intraspinal surgery or trauma |
| Any central nervous system neoplasm, arteriovenous malformation, or aneurysm |
| Known severe bleeding diathesis |
| Current severe uncontrolled hypertension (systolic > 180 mm Hg and/or diastolic > 110 mm Hg on repeated readings) |
| Known or suspected pregnancy or child bearing potential |
| Recent (≤3 mos) eye surgery |
| Inability to undergo surgical procedure, e.g., contraindication to anesthesia, severe cardiac disease, etc. |
| Recent puncture (within 10 days) of noncompressible vessel |
| Participation in another research protocol within the last 30 days |
| Relative |
| Patients with recent (≤3 weeks) vascular surgery |
| Recent (within 10 days) major non-vascular surgery |
| Significant liver dysfunction |
| History of internal (GI or GU) bleeding or other significant bleeding within the past 10 days |
| High likelihood of left heart thrombus, acute pericarditis or subacute bacterial endocarditis |
| Recent trauma within the past 10 days |
| Asymptomatic cerebrovascular disease |
| Diabetic or hemorrhagic retinopathy (grade III or IV) |
| Hemostatic defects, e.g., those secondary to severe hepatic or renal disease |
| Fewer than 100,000 platelets/$mm^3$ |
| Septic thrombophlebitis or occluded AV cannula at a seriously infected site |
| Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location |
| Severe ischemia, which in the judgement of the treating physician requires immediate operative intervention |

ter, and all patients gave written informed consent for randomization. Thirty-one centers from North America participated in this trial.

Absolute criteria for exclusion were defined as conditions that, if present, excluded the patient from entry into the study because of a prohibitive risk of a complication. Relative exclusion criteria were defined as conditions that, if present, indicated increased risk of treatment, and in whom the investigator should exercise good clinical judgment regarding patient entry. The exclusion criteria are listed in Table 1.

Before treatment assignment, the optimal surgical revascularization procedure was documented and subsequently compared to the procedure that was performed in both the surgical and thrombolysis groups.

On entry and during follow-up, the grade and clinical category of limb ischemia was assessed according to the SVS/ISCVS classification.[18] (Table 2)

## Investigators

Participating physicians were all board certified in their respective specialties—i.e., general surgery, radiology or cardiology—and involved regularly in the treatment of peripheral vascular disease.

## Randomization and Treatment Strategies

The investigators and study coordinators telephoned a 24-hour/day, 7-day/week randomization center (Collaborative Studies Coordinating Center, Department of Biostatistics, University of North Carolina, Chapel Hill, NC) to verify patient eligibility, specify planned surgical procedures, and receive treatment assignments. Patients were stratified by clinical center and were assigned to one of the following three treatment groups: 1) surgical revascularization, 2) rt-PA, or 3) UK. (Fig. 1)

During randomization, patients were stratified for native artery occlusion, bypass graft occlusion, or unreconstructible vascular disease. Unreconstructable vascular disease was characterized by the lack of an adequate vessel to receive a bypass graft and determined by an appropriately performed arteriogram, an ankle/brachial index or pulse waveform, or toe pressure consistent with limb-threatening ischemia (Grade II or III, Category 4–5).[18]

## Surgical Revascularization

The optimal surgical revascularization procedure was determined by the attending surgeon and documented before randomization. For patients with bypass graft occlusion, it was specified whether thrombectomy and graft revision or graft replacement was planned. For patients with infrainguinal native arterial occlusions, investigators were encouraged to bypass with autogenous material as the procedure of choice. However, selected lesions of the aorto-iliac system or segmental occlusions of the femoral arteries might be treated preferably with endarterectomy. It was understood that bypass of the aorto-iliac or iliofemoral segments would be performed with prosthetic material (Dacron or polytetrafluoroethylene).

The planned surgical intervention was compared with the actual procedure performed in operated patients, and contrasted with the intervention performed after thrombolysis. Operative and other procedures were ranked in order of decreasing level of intervention, as listed in Table 3.

**Table 2. SVS/ISCVS CLASSIFICATION OF CHRONIC LIMB ISCHEMIA**

| Grade | Category | Clinical Description | Objective Criteria |
|---|---|---|---|
| 0 | 0 | Asymptomatic (no hemodynamically significant occlusive disease) | Normal treadmill/stress test |
| I | 1 | Mild claudication | Completes treadmill exercise* AP after exercise <50 mm Hg but >25 mm Hg less than brachial BP |
| | 2 | Moderate claudication | Between categories 1 and 3 |
| | 3 | Severe claudication | Cannot complete treadmill exercise and AP after exercise <50 mm Hg |
| II | 4 | Ischemic rest pain | Resting AP <60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile; TP <40 mm Hg |
| III | 5 | Minor tissue loss (nonhealing ulcer, focal gangrene with diffuse pedal ischemia) | Resting AP <40 mm Hg, flat or barely pulsatile ankle or metatarsal PVR; TP <30 mm Hg |
| | 6 | Major tissue loss (extending above TM level, functional foot no longer salvageable) | Same as category 5 |

AP = ankle pressure; BP = brachial pressure; PVR = pulse volume recording; TP = toe pressure; TM = transmetatarsal.
* Five minutes at 2 mph on a 12% incline.
Reprinted with permission of Rutherford RB, Flanigan DP, Gupta SK, et al. Suggested standards for reports dealing with lower estremity ischemia. J Vasc Surg 1986; 4:80–94.

## Thrombolysis

After randomization to either rt-PA or UK, a guide wire was passed into (or through) the occlusion, and an infusion catheter was imbedded into the occluded vessel.

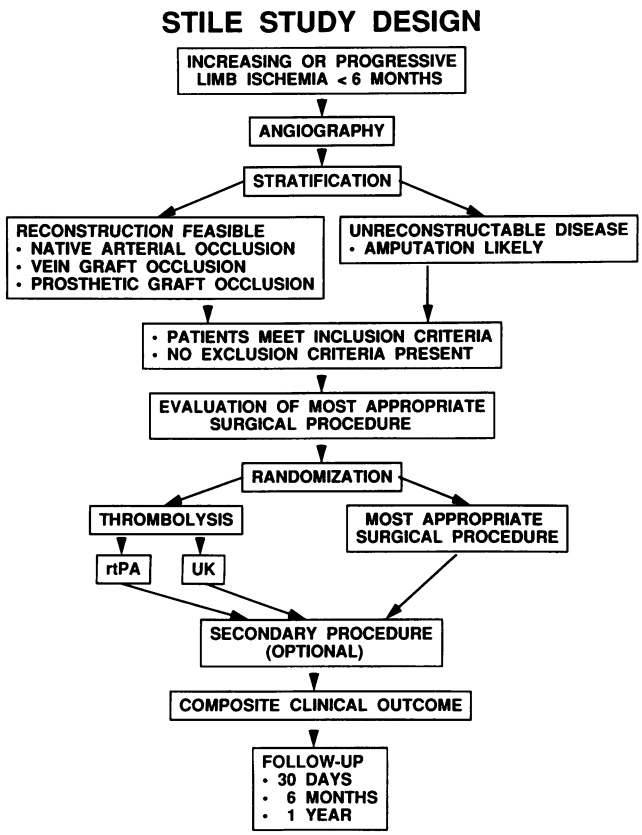


**Figure 1.** Algorithm of STILE Study design

If the infusion catheter was not imbedded into the occlusion, the thrombolytic agent was not infused, and the patient was considered a treatment failure on an intent-to-treat basis. Results of rt-PA and UK were analyzed separately to evaluate for differences in efficacy and safety, The rt-PA and UK results were combined and reported as the thrombolysis group.

## rt-PA

Catheter-directed thrombolysis with rt-PA was initiated with 0.1 mg/kg/hr for up to 12 hours. During the trial, clinical information became available that indicated that a dose of 0.05 mg/kg/hr was equally effective and associated with fewer bleeding complications. Therefore, the dose of 0.05 mg/kg/hr was adopted on August 9, 1992. Recombinant tissue plasminogen activator was not administered longer than 12 hours, and the total dose could not exceed 100 mg.

**Table 3. INTERVENTIONAL PROCEDURES IN ORDER OF INCREASING INTERVENTION**

| |
|---|
| No intervention performed |
| Further thrombolysis |
| Intravascular mechanical repair of a native vessel or existing bypass graft, i.e., balloon angioplasty |
| Thrombectomy or endarterectomy of a native vessel or thrombectomy and revision/repair on an existing bypass graft |
| Placement of a new bypass graft or replacement of an existing graft |
| Transmetatarsal amputation or loss of digit(s) |
| Below knee amputation |
| Above knee amputation |

### Uronkinase

Catheter-directed thrombolysis with UK was initiated with a 250,000-unit bolus followed by 4000 units/min for 4 hours, followed by 2000 units/min for up to an additional 32 hours.

Additionally, patients randomized to either of the thrombolysis arms received 5000 units of heparin as an intravenous bolus at the time of thrombolysis, followed by 1000 units/hr intravenously, which was titrated to maintain the activated partial thromboplastin time of 1.5 to 2.0 times control. Intra-arterial heparin was administered according to individual institutional guidelines. Heparin was continued until either 1) a contraindication to heparin therapy existed, or 2) optimal postthrombolytic management was implemented. Patients randomized to thrombolysis also received 325 mg of aspirin orally at the time of randomization, then daily.

Patients receiving catheter-directed thrombolysis had arteriography performed at 4 hours, 8 hours, and at the end of study drug infusion. All patients were treated in the radiology suite, in a cardiac catheterization laboratory, or in an intensive care unit setting. All patients received routine baseline studies that included chest x-rays, electrocardiograms, complete blood counts, fibrinogens, prothrombin times, and activated partial thromboplastin times. Routine blood studies were performed at the end of study drug infusions. Clinical assessment of vascular perfusions were recorded at the end of treatment and at 30 days, 6 months, and 1 year.

### Secondary/Subsequent Procedures

After successful study treatment, i.e., patency restored by thrombolysis or surgery, some patients required "secondary" procedures, to ensure the lasting success of the primary intervention. Secondary procedures are those that ordinarily would be considered necessary to complete the initial revascularization strategy and were performed at the discretion of the investigator. Examples of secondary procedures include approved interventional therapy (e.g., balloon angioplasty or atherectomy) as well as standard surgical intervention (e.g., endarterectomy, patch angioplasty, or lysis of a retained valve cusp), but did not include unapproved procedures, such as intravascular laser therapy. If the primary therapy failed to restore patency to the target artery or bypass graft or if reocclusion occurred and an alternative revascularization procedure was required, it was termed a subsequent procedure. By definition, all subsequent procedures followed failed primary intervention. Examples of subsequent procedures are thrombectomy or placement of a new bypass graft.

### Eligible Nonrandomized Patients (ENR)

Patients treated by study investigators who met eligibility criteria, but were not randomized into this study and were treated outside of this protocol were recorded, and their demographic characteristics were analyzed.

## PRIMARY ENDPOINT

### Composite Clinical Outcome

The primary endpoint for analysis was the occurrence of at least one event of a composite clinical outcome during the first 30 days after treatment. The composite clinical outcome also will be evaluated at 6 months and 1 year after therapy. The following list contains the components of the composite clinical outcome. The occurrence of any of these events was considered an adverse outcome, regardless of etiology, and the patient was classified as reaching a primary endpoint.

The components of the composite clinical outcome include:

1. Ongoing or recurrent ischemia—failure of the revascularization procedure to improve perfusion, or thrombosis of an initially successful procedure;
2. Death or major amputation (above knee or below knee amputation);
3. Life-threatening hemorrhage, either intracranial or blood loss-producing hypotension, requiring resuscitation;
4. Perioperative complications—i.e., cerebrovascular accident, myocardial infarct, pulmonary edema, congestive heart failure;
5. Renal failure requiring dialysis;
6. Serious anesthesia-related complications;
7. Vascular complications, e.g., dissection, perforation, pseudoaneurysm, or occlusion requiring unplanned or emergent surgical repair;
8. Postinterventional wound complications; wound infection requiring systemic antibiotics, or dedicated wound care or hematoma requiring drainage, re-exploration or blood transfusion.

### Clinical Improvement and Reduction in Surgery

In addition to the composite clinical outcome, improvement in patient's clinical outcome was defined as improvement of at least one clinical category (Table 2) at the 30-day, 6-month and 1-year time points.[18] Patients reaching a primary endpoint who have persistent or recurrent ischemia were offered additional revascularization procedures at the discretion of their attending physician. The impact of catheter-directed thrombolysis on

reduction of required surgical revascularization was evaluated by comparing the actual surgical procedure performed to that planned before randomization. A reduction in surgical revascularization was defined as a decrease of at least one level of intervention from the procedure originally planned. (Table 3)

### Patency and Perfusion Status

Vascular patency and perfusion were defined angiographically and noninvasively. The criterion for angiographic patency was restoration of luminal continuity. Hemodynamic parameters of perfusion were assessed objectively with segmental limb pressures and pulse volume recordings. The criterion for improved perfusion was defined as an increase of ankle brachial index of 0.1 or more.

## OTHER ENDPOINTS

### Duration of Ischemia

Analyzing results by duration of ischemic deterioration was not preplanned and not part of initial protocol stratification. However, observation of the data indicated a consistency of outcome and suggested that such subgroup analysis would be valuable.

### Per-Protocol Analyses

Although conclusions are based on intention-to-treat analysis, per-protocol analyses (patients receiving treatment specified at randomization) also were performed.

### Length of Hospitalization

The length of hospitalization from treatment to discharge was tabulated and stratified by duration of limb ischemia. Eighteen patients remained hospitalized at the time of their 30-day follow-up; however, the distribution of those with extended stays was similar to treatment group stratification (7 surgery and 11 thrombolysis). For the purpose of this calculation, a 30-day length of hospitalization was used for those with extended stays.

### Statistical Analysis

Patient population and sample size estimates were made after consultation with a panel of experts from vascular surgery, interventional radiology, vascular medicine, and cardiology. The required sample size was based on estimates of the rates of mortality, amputation, major morbidity, and ongoing/recurrent ischemia from the published literature and the vast clinical experience of the panel. As a result, a required sample size of approximately 1000 patients was estimated.

The primary hypothesis of this trial was that there would be a difference between the surgical and thrombolysis groups in the event rate of the composite clinical outcome at 30 days of follow-up. A stratified log rank statistic[19] (stratified by type of occluded vessel) was used to compare the event-free survival curves for the two groups in an intention-to-treat analysis.

The protocol specified two interim analyses after data were available for the primary endpoint on approximately 300 and 600 patients. The interim analyses were reviewed by an independent data and safety monitoring committee. They chose to use a Lan-deMets boundary[20] as the formal statistical guideline at interim analyses.

The other analyses reported are based on Cochran-Mantel-Haenszel chi square statistics[21] for stratified $2 \times 2$ tables, the Fisher exact test[22] for simple $2 \times 2$ tables, and Breslow-Day chi square statistics[23] for testing for treatment by subgroup interactions.

### Data Management

A detailed case report form was completed for each patient. The accuracy of the case report forms were verified by study monitors, who checked them with the patients' medical records. The case report forms then were forwarded to the data coordinating center (Collaborative Studies Coordinating Center, Department of Biostatistics, University of North Carolina, Chapel Hill, NC) for evaluation and the generation of queries about missing or inconsistent data and subsequent data entry. The data then were tabulated and analyzed.

The data coordinating center operated independently of the investigators and the sponsor. Although monthly reports of patient entry were distributed to all investigators, outcome analyses were not available to either the investigators or sponsor and were reported only to the Data and Safety Monitoring Committee at the scheduled interim analyses.

### Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee functioned independently from the investigators and the sponsor. It was composed of five members, representing the specialties of vascular surgery, interventional radiology, cardiology and vascular medicine. The role of the Data and Safety Monitoring Committee was to review safety and efficacy data, study progress at each interim analysis, and make recommendations regarding the conduct of the study.

### Relationship with Sponsor

As part of the conduct of the study, the organizers designed specific measures to avoid financial conflict of interest. All members of the steering committee, the Data and Safety Monitoring Committee, Data Coordinating Center, and all participating investigators, declared in writing that neither they nor their immediate family members had any financial interest with the sponsor. This included equity interest in the company, consulting relationships, honoraria or reimbursement for travel expenses other than those associated with investigator meetings.

## RESULTS

A primary endpoint was determined by a patient experiencing one of the components of the composite clinical outcome within 30 days of treatment. Follow-up information was obtained for 392 of the 393 randomized patients. At the time of this report, 6-month follow-up data for the endpoints of amputation and death were available for 356 patients (91%); 30 patients have withdrawn, and 7 were unable to be observed for follow-up. Patient demographics are listed in Table 4, and are similar for each treatment group. Worthy of note is the long duration of worsening ischemia (mean 50.3 days), older patient population (43% ≥ 70 years), and severity of ischemia (69% with limb threatening ischemia).

### Duration of Worsening Ischemia

Thirty per cent were randomized within 14 days of worsening ischemia, and 44% of the patients had symptoms for 1 month or more before randomization; 26% had symptoms for 2 months or more. Symptoms occurred in patients with bypass graft occlusion earlier than patients with native arterial occlusion. Symptoms of worsened ischemia appeared within 14 days for 48% of patients with bypass graft occlusion compared with only 24% of patients with native arterial occlusion. Only 28% of patients with occluded bypass grafts were symptomatic for 30 days or longer, whereas 52% of patients with native arterial occlusion complained of worsening symptoms for 30 days or more before randomization.

### Withdrawals

Twenty-eight patients (7.1%) were withdrawn after randomization—i.e., 16 (11.1%) of the surgical group and 12 (4.8%) of the thrombolysis group (p = NS). Sixty-seven per cent of the withdrawals were a result of patient preference, and 33% were a result of physician preference, with equal distribution within the thrombolysis and surgery groups. Although the demographics of withdrawn patients generally were similar, the age of withdrawn patients assigned to surgery tended to be higher than those withdrawn from the thrombolysis group (68 years of age *vs.* 60 year of age, $p < 0.1$).

### ENR Patients

One hundred seventy-seven ENR patients were recorded. Randomized patients were more likely to be of minority backgrounds, have more severe ischemia, and histories of more severe vascular disease ($p < 0.05$) compared with ENR patients.

### Primary Outcome

Primary analysis was performed on an intent-to-treat basis (Table 5). The event rate for the composite clinical outcome for thrombolysis patients was 61.7% compared with 36.1% for surgical patients ($p < 0.001$). Patients randomized to catheter-directed thrombolysis had significantly greater ongoing/recurrent ischemia (54% *vs.* 25.7%; $p < 0.001$), life-threatening hemorrhage (5.6% *vs.* 0.7%; $p = 0.014$), and more vascular complications (9.7% *vs.* 3.5%; $p = 0.032$) compared with surgical patients. Three of the patients with life-threatening hemorrhages sustained an intracranial bleed, for an incidence of 1.2%. Two patients were randomized to rt-PA, and one was randomized to UK. There was no difference overall in mortality or major amputations between thrombolysis and surgical groups.

### rt-PA *Versus* UK

There was no difference in efficacy or bleeding complications in patients receiving rt-PA compared with UK. However, there were more side effects of nausea and vomiting for patients receiving UK (p = NS).

### Technical Results of Thrombolysis

Technical failures accounted for a large proportion of lytic failures. Failure of catheter placement occurred in 28% of patients randomized to lysis, 41% with occluded bypass grafts and 22% with occluded native arteries (p = NS). No difference in catheter penetration of the occluded vessel was observed when stratified for duration of ischemia. Once infusion was instituted, patency was restored to 81% of bypass grafts compared with 69% of native arteries (p = NS). There was a trend toward higher overall patency in the thrombolysis group if the guide wire could be advanced through the occluded vessel (67.3% *vs.* 53.8%; $p = 0.105$). Translesion passage of the guide wire in native arteries was associated with higher

**Table 4. DEMOGRAPHIC CHARACTERISTICS BY TREATMENT**

| | Surgery (N = 144) | | rt-PA (N = 137) | | UK (N = 112) | | Overall (N = 393) | |
|---|---|---|---|---|---|---|---|---|
| **Stratum** | **No.** | **Percent** | **No.** | **Percent** | **No.** | **Percent** | **No.** | **Percent** |
| Native artery | 97 | 67.4 | 91 | 66.4 | 74 | 66.1 | 262 | 66.7 |
| Bypass graft | 43 | 29.9 | 39 | 28.5 | 33 | 29.5 | 115 | 29.3 |
| URVD | 4 | 2.8 | 7 | 5.1 | 5 | 4.5 | 16 | 4.1 |
| TOTAL | 144 | 100.0 | 137 | 100.0 | 112 | 100.0 | 393 | 100.0 |
| Duration of ischemia (days)* | | 52.5 | | 51.7 | | 45.9 | | 50.3 |
| Age (yrs)* | | 65.3 | | 65.4 | | 64.9 | | 65.2 |
| Height (cm)* | | 169.1 | | 169.6 | | 166.9 | | 168.7 |
| Weight (kg)* | | 74.1 | | 74.0 | | 73.0 | | 73.7 |
| Sex | | | | | | | | |
| Female | 39 | 27.1 | 43 | 31.6 | 42 | 37.5 | 124 | 31.6 |
| Male | 105 | 72.9 | 93 | 68.4 | 70 | 62.5 | 268 | 68.4 |
| Race | | | | | | | | |
| Caucasian | 104 | 72.2 | 100 | 73.5 | 88 | 78.6 | 292 | 74.5 |
| Black | 26 | 18.1 | 20 | 14.7 | 17 | 15.2 | 63 | 16.1 |
| Hispanic | 13 | 9.0 | 15 | 11.0 | 7 | 6.3 | 35 | 8.9 |
| Other | 1 | 0.7 | 1 | 0.7 | 0 | 0.0 | 2 | 0.6 |
| Age (mean yrs) | | | | | | | | |
| <40 | 1 | 0.7 | 0 | 0.0 | 3 | 2.7 | 4 | 1.0 |
| 40–49 | 15 | 10.4 | 13 | 9.6 | 10 | 8.9 | 38 | 9.7 |
| 50–59 | 30 | 20.8 | 25 | 18.4 | 20 | 17.9 | 75 | 19.1 |
| 60–69 | 34 | 23.6 | 40 | 29.4 | 31 | 27.7 | 105 | 26.8 |
| 70–79 | 45 | 31.3 | 51 | 37.5 | 40 | 35.7 | 136 | 34.7 |
| 80+ | 19 | 13.2 | 6 | 4.4 | 7 | 6.3 | 32 | 8.2 |
| Vascular diseases | | | | | | | | |
| Coronary artery disease | 56 | 38.9 | 48 | 35.3 | 40 | 35.7 | 144 | 36.7 |
| Diabetes | 60 | 41.7 | 58 | 42.6 | 43 | 38.4 | 161 | 41.1 |
| Hypertension | 74 | 51.4 | 78 | 57.8 | 59 | 52.7 | 211 | 53.8 |
| Smoker | 118 | 81.9 | 110 | 80.9 | 88 | 78.6 | 316 | 80.6 |
| Peripheral vascular symptoms—study limb | | | | | | | | |
| Intermittent claudication | 118 | 81.9 | 110 | 80.9 | 83 | 74.1 | 311 | 79.3 |
| Rest pain | 79 | 54.9 | 71 | 52.2 | 71 | 63.4 | 221 | 56.4 |
| Ulcer/necrotic tissue | 40 | 27.8 | 49 | 36.0 | 39 | 34.8 | 128 | 32.7 |
| Neuropathy | 38 | 26.4 | 28 | 20.6 | 30 | 26.8 | 96 | 24.5 |
| Previous amputation | 11 | 7.6 | 8 | 5.9 | 10 | 8.9 | 29 | 7.4 |
| Previous bypass surgery | 57 | 39.6 | 55 | 40.4 | 48 | 42.9 | 160 | 40.8 |
| Peripheral vasclar symptoms—other limb | | | | | | | | |
| Intermittent claudication | 54 | 37.5 | 40 | 29.4 | 36 | 32.1 | 130 | 33.2 |
| Rest pain | 11 | 7.6 | 7 | 5.1 | 7 | 6.3 | 25 | 6.4 |
| Ulcer/necrotic tissue | 3 | 2.1 | 4 | 2.9 | 3 | 2.7 | 10 | 2.6 |
| Neuropathy | 12 | 8.3 | 7 | 5.1 | 11 | 9.8 | 30 | 7.7 |
| Previous amputation | 14 | 9.7 | 16 | 11.8 | 7 | 6.3 | 37 | 9.4 |
| Previous bypass surgery | 32 | 22.2 | 33 | 24.3 | 21 | 18.8 | 86 | 21.9 |

$p > 0.05$ for comparisions among treatment groups.
* Means.

**Table 5. SURGERY *VS.* THROMBOLYSIS: COMPOSITE CLINICAL OUTCOME AT 1-MONTH (INTENTION-TO-TREAT ANALYSIS)**

| Event | Surgery (N = 144) | | Thrombolysis (N = 248) | | p Value |
|---|---|---|---|---|---|
| | No. | Percent | No. | Percent | |
| Composite clinical outcome | 52 | 36.1 | 153 | 61.7 | <0.001 |
| Death | 7 | 4.9 | 10 | 4.0 | 0.693 |
| Major amputation | 9 | 6.3 | 13 | 5.2 | 0.685 |
| Ongoing/recurrent ischemia | 37 | 25.7 | 134 | 54.0 | <0.001 |
| Major morbidity | 23 | 16.0 | 51 | 20.6 | 0.266 |
| Life-threatening hemorrhage | 1 | 0.7 | 14 | 5.6 | 0.014 |
| Perioperative complications | 13 | 9.0 | 14 | 5.6 | 0.200 |
| Renal failure | 1 | 0.7 | 3 | 1.2 | 0.629 |
| Anesthesia complications | 1 | 0.7 | 0 | 0.0 | 0.188 |
| Vascular complication | 5 | 3.5 | 24 | 9.7 | 0.024 |
| Post-intervention wound complication | 4 | 2.8 | 13 | 5.2 | 0.249 |

subsequent patency compared with partial passage (66% *vs.* 44%; p = 0.033); this effect was not seen in occluded bypass grafts.

## Per-Protocol Analysis

Table 6 presents the composite clinical outcome in patients treated per protocol, defined as those actually receiving treatment specified at randomization. When a catheter was positioned successfully and a lytic agent infused, the results in the group of patients undergoing thrombolysis improved, but not enough to alter primary conclusions.

To evaluate the durability of successful primary treatment, the results of patients who had patency established after assigned treatment are shown in Table 7. Patients who underwent thrombolysis had a higher event rate for the composite clinical outcome (p = 0.011) because of a higher rate of recurrent ischemia (p = 0.010) and major morbidity (p = 0.021).

## Outcome by Vessel Type

There were no differences in composite clinical outcome within treatment groups in patients with native artery or those with occluded bypass grafts (Table 8). Patients who underwent operations had significantly less ongoing/recurrent ischemia in both subgroups com-

**Table 6. SURGERY *VS.* THROMBOLYSIS: COMPOSITE CLINICAL OUTCOME AT 1-MONTH (PER-PROTOCOL ANALYSIS—PATIENTS RECEIVING TREATMENT SPECIFIED AT RANDOMIZATION)**

| Event | Surgery (N = 127) | | Thrombolysis (N = 194) | | p Value |
|---|---|---|---|---|---|
| | No. | Percent | No. | Percent | |
| Composite clinical outcome | 44 | 34.6 | 107 | 55.2 | <0.001 |
| Death | 6 | 4.7 | 9 | 4.7 | 0.938 |
| Major amputation | 8 | 6.3 | 10 | 5.2 | 0.726 |
| Ongoing/recurrent ischemia | 30 | 23.6 | 88 | 45.4 | <0.001 |
| Major morbidity | 20 | 15.7 | 43 | 22.2 | 0.171 |
| Life-threatening hemorrhage | 1 | 0.8 | 12 | 6.2 | 0.019 |
| Perioperative complications | 11 | 8.7 | 12 | 6.2 | 0.365 |
| Renal failure | 1 | 0.8 | 3 | 1.6 | 0.577 |
| Anesthesia complications | 0 | 0.0 | 0 | 0.0 | — |
| Vascular complication | 4 | 3.1 | 22 | 11.3 | 0.010 |
| Post-intervention wound complication | 4 | 3.1 | 10 | 5.2 | 0.375 |

**Table 7. SURGERY *VS.* THROMBOLYSIS: COMPOSITE CLINICAL OUTCOME AT 1 MONTH (PER-PROTOCOL ANALYSIS—RESTRICTED TO PATIENTS IN WHOM PATENCY WAS ESTABLISHED**

| | Surgery (N = 106) | | Thrombolysis (N = 128) | | |
|---|---|---|---|---|---|
| Event | No. | Percent | No. | Percent | p Value |
| Composite clinical outcome | 24 | 22.6 | 49 | 38.3 | 0.011 |
| Death | 3 | 2.8 | 6 | 4.7 | 0.474 |
| Major amputation | 2 | 1.9 | 3 | 2.3 | 0.805 |
| Ongoing/recurrent ischemia | 14 | 13.2 | 35 | 27.3 | 0.010 |
| Major morbidity | 13 | 12.3 | 31 | 24.2 | 0.021 |
| Life-threatening hemorrhage | 1 | 0.9 | 10 | 7.8 | 0.014 |
| Perioperative complications | 6 | 5.7 | 10 | 7.8 | 0.532 |
| Renal failure | 1 | 0.9 | 3 | 2.3 | 0.422 |
| Anesthesia complications | 0 | 0.0 | 0 | 0.0 | — |
| Vascular complication | 2 | 1.9 | 14 | 10.9 | 0.006 |
| Post-intervention wound complication | 4 | 3.8 | 7 | 5.5 | 0.532 |

Patent is defined as follows for thrombolytic patients: luminal reconstitution through occluded segments into distal vasculature or in continuity with the foot.
Patent is defined as follows for surgical patients: perfusion established at the end of primary procedure, documented by operative arteriogram and improvement of ABI, and no subsequent procedure required.

pared with patients who underwent thrombolysis. In surgical patients, there was a higher amputation rate in those with occluded bypass grafts (p = 0.002) and a trend toward a higher mortality with native arterial occlusion (p = 0.064). These outcome differences were not observed in thrombolysis patients.

**Table 8. SURGERY *VS.* THROMBOLYSIS: OUTCOME AT 1 MONTH BY VESSEL TYPE (INTENTION-TO-TREAT ANALYSIS)**

| | | Surgery (N = 144) | | Thrombolysis (N = 248) | | |
|---|---|---|---|---|---|---|
| Stratum | Event | No. | Percent | No. | Percent | p Value |
| Native artery | (Count) | 98 | — | 170 | — | |
| | Composite clinical outcome | 34 | 34.7 | 106 | 62.4 | <0.001 |
| | Death | 7 | 7.1 | 7 | 4.1 | 0.285 |
| | Major amputation | 2 | 2.0 | 7 | 4.1 | 0.364 |
| | Ongoing/recurrent ischemia | 23 | 23.5 | 93 | 54.7 | <0.001 |
| | Major morbidity | 18 | 18.4 | 37 | 21.8 | 0.508 |
| Bypass graft | (Count) | 46 | — | 78 | — | |
| | Composite clinical outcome | 18 | 39.1 | 47 | 60.3 | 0.023 |
| | Death | 0 | 0.0 | 3 | 3.8 | 0.180 |
| | Major amputation | 7 | 15.2 | 6 | 7.7 | 0.188 |
| | Ongoing/recurrent ischemia | 14 | 30.4 | 41 | 52.6 | 0.017 |
| | Major morbidity | 5 | 10.9 | 14 | 17.9 | 0.292 |
| Overall | (Count) | 144 | — | 248 | — | |
| | Composite clinical outcome | 52 | 36.1 | 153 | 61.7 | <0.001 |
| | Death | 7 | 4.9 | 10 | 4.0 | 0.698 |
| | Major amputation | 9 | 6.3 | 13 | 5.2 | 0.673 |
| | Ongoing/recurrent ischemia | 37 | 25.7 | 134 | 54.0 | <0.001 |
| | Major morbidity | 23 | 16.0 | 51 | 20.6 | 0.263 |

**Table 9. SURGERY *VS.* THROMBOLYSIS: OUTCOME AT 1 MONTH BY DURATION OF ISCHEMIA (INTENTION-TO-TREAT ANALYSIS)**

| Event | Surgery (N = 135) No. | Surgery (N = 135) Percent | Thrombolysis (N = 240) No. | Thrombolysis (N = 240) Percent | p Value |
|---|---|---|---|---|---|
| Duration of ischemia: 0–14 days | | | | | |
| (Count) | 39 | | 73 | | |
| Composite clinical outcome | 21 | 53.8 | 43 | 61.4 | 0.459 |
| Death | 2 | 5.1 | 3 | 4.3 | 0.810 |
| Major amputation | 7 | 17.9 | 4 | 5.7 | 0.061 |
| Ongoing/recurrent ischemia | 15 | 38.5 | 34 | 48.6 | 0.328 |
| Major morbidity | 10 | 25.6 | 15 | 21.4 | 0.598 |
| Life-threatening hemorrhage | 0 | 0.0 | 4 | 5.7 | 0.157 |
| Perioperative complications | 8 | 20.5 | 7 | 10.0 | 0.098 |
| Renal failure | 0 | 0.0 | 0 | 0.0 | — |
| Anesthesia complications | 0 | 0.0 | 0 | 0.0 | — |
| Vascular complications | 1 | 2.6 | 5 | 7.1 | 0.293 |
| Post-intervention wound complications | 1 | 2.6 | 5 | 7.1 | 0.293 |
| Duration of ischemia: >14 days | | | | | |
| (Count) | 96 | | 170 | | |
| Composite clinical outcome | 28 | 29.2 | 107 | 62.9 | <0.001 |
| Death | 4 | 4.2 | 5 | 2.9 | 0.617 |
| Major amputation | 2 | 2.1 | 9 | 5.3 | 0.218 |
| Ongoing/recurrent ischemia | 20 | 20.8 | 99 | 58.2 | <0.001 |
| Major morbidity | 13 | 13.5 | 34 | 20.0 | 0.169 |
| Life-threatening hemorrhage | 1 | 1.0 | 9 | 5.3 | 0.080 |
| Perioperative complications | 5 | 5.2 | 7 | 4.1 | 0.712 |
| Renal failure | 1 | 1.0 | 3 | 1.8 | 0.618 |
| Anesthesia complications | 1 | 1.0 | 0 | 0.0 | — |
| Vascular complications | 4 | 4.2 | 18 | 10.6 | 0.063 |
| Post-intervention wound complications | 3 | 3.1 | 8 | 4.7 | 0.526 |

## Ongoing/Recurrent Ischemia

Persistent or recurrent ischemia was a strong predictor of major amputation and additional major morbidity. Twenty-five per cent of patients with ongoing or recurrent ischemia had additional major complications, and 10% had major amputation, compared with 13% and 2%, respectively, for those without ongoing/recurrent ischemia ($p < 0.002$ and $p < 0.001$).

## Duration of Ischemia

Outcome by treatment group was stratified by duration of ischemia (Table 9). There was no difference in composite clinical outcome in patients with acute ischemia (0–14 days of worsening ischemia); however, surgical patients had more major amputations (17.9%) than patients who underwent thrombolysis (5.7%; $p = 0.061$). In the acutely ischemic patients, there was a high rate of ongoing/recurrent ischemia in both surgical and thrombolysis groups, (38.5% and 48.6%, respectively; p = NS). The opposite was observed in patients with more chronic conditions, i.e., surgically treated patients had less ongoing/recurrent ischemia than patients who underwent thrombolysis (20.8% *vs.* 58.2%; $p < 0.001$). There also was a trend toward a reduction in major amputation for surgically treated patients.

## Reduction in Planned Revascularization Procedure

Of the patients randomized to catheter-directed thrombolysis, 55.8% had a major reduction in their planned revascularization procedure compared with 5.5% of surgical patients ($p < 0.001$) (Table 10). Patients whose thrombolysis outcome permitted a reduction in their planned procedure had a 90.1% amputation-free survival at 6 months compared with a 71.1% amputation-free survival for patients without a reduction in planned procedure ($p < 0.05$).

**Table 10. SURGERY *VS.* THROMBOLYSIS: PLANNED *VS.* ACTUAL INTERVENTION, REDUCTION IN SEVERITY OF PROCEDURE BY TREATMENT**

| Reduction in Procedure | Surgery | | Thrombolysis | | |
|---|---|---|---|---|---|
| | No. | Percent | No. | Percent | p Value |
| Reduction by at least 1 level | 7 | 5.5 | 91 | 55.8 | <0.001 |
| No reduction | 120 | 94.5 | 72 | 44.2 | — |

Thrombolysis group restricted to patients in whom catheter was imbedded in occlusion.

## Bleeding Complications

Hemorrhage is the most worrisome complication of thrombolytic therapy. Laboratory and infusion parameters in patients with and without hemorrhagic complications are listed in Table 11. There was no difference in the amount of lytic agent or heparin infused between the two groups; however, there is an apparent difference in response to the drugs. Those with bleeding complications had a significantly lower plasma fibrinogen at the end of infusion ($p = 0.01$) and showed a trend toward a prolonged prothrombin time and activated partial thromboplastin time.

## Clinical Outcome Classification

Despite an increased incidence of ongoing/recurrent ischemia in patients undergoing thrombolysis, the clinical outcome classification at 30 days was no different in patients randomized to thrombolysis compared to those randomized to surgery. (Table 12)

## Length of Hospitalization

In the patient group with acute symptom deterioration (0–14 days), surgical patients had a mean hospital stay of 14.3 days, whereas thrombolysis patients had a mean hospital stay of 9.7 days ($p = 0.04$). Patients with chronic ischemia (> 14 days) did not demonstrate a difference in length of hospital stay between the two treatment groups.

## Six Month Follow-Up

Six-month data were available for the two major endpoints of amputation and death (Table 13). Although there was no difference between the treatments overall, there were differences in treatment strategies when stratified by duration of ischemia. Surgery was more effective in patients with more chronic symptoms and less effective in the acute group, whereas lysis was equally effective in both groups. Within the group of patients with acute symptoms (0–14 days), there was significant advantage for reduction in death and amputation with thrombolysis compared with surgery (15.3% *vs.* 37.5%; $p = 0.01$). In the group with chronic symptoms (>14 days), there was a nonsignificant trend toward an advantage for surgery in the combined death/amputation outcome (9.9% *vs.* 17.8%; $p = 0.08$).

Differences were most apparent when focusing on major amputation, which in the acutely ischemic patients occurred in 30% of patients who underwent operations compared with 11% of patients who underwent thrombolysis ($p = 0.02$). These trends in limb loss were reversed in the chronically ischemic patients, with only 3% of surgical patients having major amputation compared with 12.1% of thrombolysis patients ($p = 0.01$).

## DISCUSSION

This study was designed as an inclusive trial that attempted to enroll the broadest possible spectrum of patients with lower extremity ischemia caused by native artery or bypass graft occlusion who had worsening of their ischemic symptoms within the previous 6 months. Therefore, by design, patients with long-standing occlusive disease and acutely ischemic patients were entered into the study. No previous study of catheter-directed thrombolysis included a suitably matched surgical group

**Table 11. LABORATORY INFUSION PARAMETERS IN THROMBOLYSIS PATIENTS BY OCCURRENCE OF MAJOR HEMORRHAGE**

| | Hemorhage | No Hemorrhage | |
|---|---|---|---|
| | Median | Median | p Value |
| Age | 70.5 | 67.0 | NS |
| Duration of ischemia (days) | 25 | 30 | NS |
| Heparin infusion rate (IU/hr) | 2,298 | 2,728 | NS |
| Total UK (1000s IU) | 1,330 | 2,420 | NS |
| UK infusion duration (hrs) | 4.7 | 16.0 | NS |
| Total rt-PA (mg) | 25 | 31 | NS |
| rt-PA infusion duration (hrs) | | | |
| End of infusion | 8.1 | 7.8 | NS |
| Fibrinogen (mg/dL) | 188 | 310 | 0.01 |
| aPTT (sec) | 114 | 58 | 0.26 |
| PT (sec) | 14.5 | 13.8 | 0.14 |

**Table 12. CLINICAL OUTCOME CLASSIFICATION AT ONE MONTH, SURGERY VS. THROMBOLYSIS**

| Clinical Outcome Classification | Surgery (N = 118) | | Thrombolysis (N = 221) | | |
|---|---|---|---|---|---|
| | No. | Percent | No. | Percent | p Value |
| Outcome improved | 93 | 78.8 | 181 | 81.9 | 0.5315 |
| +3 Markedly improved | 51 | 43.2 | 101 | 45.7 | |
| +2 Moderately improved | 36 | 30.5 | 65 | 29.4 | |
| +1 Minimally improved | 6 | 5.1 | 15 | 6.8 | |
| Outcome not improved | 25 | 21.2 | 40 | 18.1 | |
| 0 No change | 16 | 13.6 | 26 | 11.8 | |
| −1 Mildly worse | 4 | 3.4 | 4 | 1.8 | |
| −2 Moderately worse | 0 | 0.0 | 5 | 2.3 | |
| −3 Markedly worse | 5 | 4.2 | 5 | 2.3 | |

for direct comparison of treatment outcome. Embolic occlusions were specifically excluded because they represent a subset of patients whose natural history and response to therapy may not be representative of patients with thrombotic occlusions.[24–26]

The complication and failure rate of patients randomized in this study are higher than most single-center reports. This was a prospectively monitored study, with endpoints defined before patient treatment and withdrawn and technical failure patients defined as treatment failures. Therefore, it was the strict definitions and protocol design rather than inadequate care that determined outcome. The durability of a strategy of catheter-directed thrombolysis depends in large part on the secondary procedure performed to treat the underlying lesion. Analyzing all patients who have initially successful primary therapy should allow one to determine lasting therapeutic efficacy. It appears that surgical reconstruction is more durable than thrombolysis.

Given the study design and the number of patients enrolled with chronic ischemia, perhaps it is not surprising that surgically treated patients had significantly less ongoing or recurrent ischemia and hemorrhagic complications than the thrombolysis group. The mean duration of worsening ischemic symptoms was 50.3 days, and 26% of the patients had ischemic deterioration for more than 2 months. Because patients with longer duration ischemia (>14 days) outnumbered those with acute ischemia (0–14 days) by approximately 2.5:1, outcome differences observed in the chronically ischemic patients would have the greatest effect on primary endpoint analysis.

Atherosclerotic plaque and well-formed thrombus was likely the underlying pathology in the chronically ischemic patients. Even with partial penetration of the catheter, a lytic agent may not be successful in many of these chronically ischemic patients because of proximal thrombus and distal atherosclerotic occlusion. Twenty-seven per cent who were randomized to thrombolysis could not have the catheter imbedded appropriately into the occluded artery or bypass graft. They were not treated with a lytic agent and were considered a failure of therapy on an intent-to-treat basis, impacting negatively on the results of thrombolysis. In clinical practice and in previous reports, such technical failures are not part of outcome analysis because they did not receive a lytic agent.

One might anticipate greater difficulty in catheter positioning for patients with long-standing occlusions; however, we observed no difference in technical success

**Table 13. SURGERY VS. THROMBOLYSIS: DEATH AND AMPUTATION OUTCOME AT 6 MONTHS, BY DURATION OF ISCHEMIA**

| | 0–14 Days | | | | | >14 Days | | | | | Overall | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Surgery | | Lysis | | | Surgery | | Lysis | | | Surgery | | Lysis | | |
| | n | % | n | % | p | n | % | n | % | p | n | % | n | % | p |
| Intent-to-treat | | | | | | | | | | | | | | | |
| (Count) | 40 | | 72 | | | 101 | | 174 | | | 141 | | 246 | | (#22, 3/19) |
| Death/amputation | 15 | 37.5 | 11 | 15.3 | 0.01 | 10 | 9.9 | 31 | 17.8 | 0.08 | 25 | 17.7 | 42 | 17.1 | 0.89 |
| Death | 4 | 10.0 | 4 | 5.6 | 0.45 | 8 | 7.9 | 12 | 6.9 | 0.81 | 12 | 8.5 | 16 | 6.5 | 0.54 |
| Major amputation | 12 | 30.0 | 8 | 11.1 | 0.02 | 3 | 3.0 | 21 | 12.1 | 0.01 | 15 | 10.6 | 29 | 11.8 | 0.87 |
| Per-protocol | | | | | | | | | | | | | | | |
| (Count) | 36 | | 50 | | | 89 | | 143 | | | 125 | | 193 | | |
| Death/amputation | 13 | 36.1 | 7 | 14.0 | 0.02 | 9 | 10.1 | 30 | 21.0 | 0.03 | 22 | 17.6 | 37 | 19.2 | 0.77 |
| Death | 4 | 11.1 | 3 | 6.0 | 0.45 | 7 | 7.9 | 12 | 8.4 | 0.99 | 11 | 8.8 | 15 | 7.8 | 0.84 |
| Major amputation | 10 | 27.8 | 5 | 10.0 | 0.04 | 3 | 3.4 | 20 | 14.0 | 0.01 | 13 | 10.4 | 25 | 13.0 | 0.60 |

rates stratified according to the duration of ischemia. Technical success rates differed substantially among clinical centers, perhaps reflecting differences in operator skill and patient sample.

The data collected on ENR patients indicate that the STILE patient sample was potentially biased toward older and more severely ischemic limbs, with 69% of randomized patients having limb-threatening ischemia. As such, these results may represent the "worst case scenario," both for thrombolysis and surgical patients.

It was recognized from the beginning that it was impractical to conduct a study designed to detect efficacy differences between rt-PA and UK. Both agents were included in this analysis to confirm anticipated similarity in efficacy and safety, and to evaluate whether subtle differences surfaced between these two treatment groups. Although there were more nausea and vomiting side effects with UK, overall outcomes with respect to efficacy and safety were similar.

Bleeding complications were more frequent in the group that underwent thrombolysis and were similar in rt-PA- and UK-treated patients. Patients who underwent thrombolysis received aspirin and heparin by protocol design, which may have contributed to hemorrhagic risk. Interestingly, patients with bleeding complications did not receive more heparin or lytic agent; however, they appeared to respond differently to the lytic agents and anticoagulation because they had a significantly lower plasma fibrinogen and a trend toward a prolonged prothrombin time and activated partial thromboplastin time. These findings differ from patients treated with systemic thrombolysis for venous thromboembolic disease.[27] The most devastating of the bleeding complications is intracranial hemorrhage. In reviewing these and other contemporary data,[27] the baseline risk of intracranial hemorrhage in this patient population appears to be 1% to 2% for either lytic agent, despite careful patient selection.

The clinical outcome classification at 30 days for patients randomized to thrombolysis is no different than those randomized to surgery. This represents treatment crossover to the planned surgical procedure in 70% of patients who failed thrombolysis.

An interesting, but perhaps not unexpected, observation was that patients who had acute ischemia had a lower amputation rate with thrombolysis than with surgical revascularization. This is consistent with the clinical experience reported by others.[11] However, in patients with more chronic limb ischemia (>14 days), there was a trend toward reduction in major amputations and a significant reduction in ongoing/recurrent ischemia in surgical patients. This differential success of thrombolysis in acutely ischemic limbs may be the result of low pressure reperfusion[28] or lysing thrombus in the outflow vascular bed, which allows more effective reperfusion at the tissue level and minimizes the "no reflow" phenomenon.[29–31] Although there can be difficulty in accurately determining the duration of occlusion based on clinical symptoms alone, patients with shorter duration and more acute symptoms are likely to be categorized more accurately than those with more chronic symptoms.

Six-month follow-up data places the treatment strategies into long-term perspective. Although there was no overall difference in mortality or major amputation, results again were separated according to duration of ischemia. In acutely ischemic patients, there was a higher amputation-free survival in patients who underwent thrombolysis ($p = 0.01$) because of improved limb salvage ($p = 0.02$), compared with surgical patients. However, the the converse was true in chronically ischemic patients, who had better limb salvage when treated surgically ($p < 0.01$).

Although a cost-benefit analysis has not been performed yet, in the subset of patients with acute ischemia (0–14 days), catheter-directed thrombolysis is likely to be both cost effective and clinically beneficial.

Because this trial was stopped based on the first interim analysis, some caution should be used in interpreting the secondary analyses. It has been shown[32] that in such cases, the conventional estimates of parameters (and corresponding p values) based on components of the primary endpoint will have some bias away from the null hypothesis. However, our presentation follows the traditional approach to reporting in such situations.

The results of this study indicate that a management scheme incorporating catheter-directed thrombolysis in patients with acute ischemia (0–14 days) and surgical revascularization for patients with chronic ischemia (>14 days) is likely to improve patient care and offer the best overall results.

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## Appendix A

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## Discussion

DR. ROBERT S. RHODES (Jackson, Mississippi): Randomized controlled trials by surgeons involving surgical procedures are rare; therefore, these investigators deserve special congratulations.

While it may seem that the study only proves what we already know, or think we know, we also live in an era where the value of specific medical procedures and practices are increasingly questioned. Health policy researchers are fond of pointing out that only 15 to 20% of medical practice is actually proven effective on the basis of studies such as the one we just heard. Thus, these results should not be trivialized.

As one might expect, there's a lot of data in the manuscript and there's a lot more to be gained by actually reading it. I'd like to focus on two points.

First, there was an overall 28% failure rate in the ability to appropriately place the catheter in patients randomized to thrombolysis. Was there significant variation in the failure rate among the institutions that participated and would the results have been the same if these failures were excluded?

I'd also like to focus on the lack of cost data and, thus, that there is no cost-effective analysis. The manuscript contains the speculation that thrombolysis is likely to be cost-effective in the subset of patients with zero to 14 days of ischemia. I presume that is on the basis that these patients had a shorter length of stay. Yet, while length of stay correlates with cost, it is not an absolute correlation. So I'd like to know a little bit more about the basis for your speculation. If you do not have specific financial data, are you considering collecting it retrospectively?

DR. ROBERT B. RUTHERFORD (Denver, Colorado): I've had the pleasure of reading this superb manuscript. This excellent study is likely to have a major impact on clinical practice, depending on the proper interpretation of its voluminous data. Therefore, I rise to pose three questions, the answers to which should add to our perspective of this trial.

First, by not eliminating initial technical failures from analysis of success, a common practice in interventional radiology and which amounted to 28% in this trial, you have provided a more sobering view of the efficacy of catheter-directed thrombolytic therapy. But could you also give us a perspective of the impact of treatment crossovers; specifically, what proportion of lytic therapy successes in your less-than-14-day group resulted from subsequent surgery, or, conversely, what percent were successfully treated by lytic therapy alone without the need for operation?

Second, many of your secondary conclusions were based on a separation of cases into less than or greater than 14 days of ischemia. Was the 14 days an arbitrary endpoint or one chosen by a retrofit of data to maximize the contrasting benefits of thrombolysis *versus* surgery?

And finally, I'm concerned lest one of your bottom-line conclusions—namely, that thrombolysis is better for acute limb ischemia of less than 14 days duration—may be indiscriminately applied to acutely threatened limbs—that is, those with persistent ischemic pain and motor or sensory loss where immediate surgery is still considered mandatory. Were any or a significant proportion of such cases included in your less-than-14-day group and, if not, are your conclusions not applicable to this critical subgroup?

I think this is a hallmark study and I appreciate the privilege of discussing it. Thank you.

DR. CALVIN B. ERNST (Detroit, Michigan): The data in this report are voluminous and merit close scrutiny; in fact, there are 12 tables that are very detailed. Consequently, I would like to focus on one aspect of this study. Dr. Comerota, I am puzzled why thrombolysis was better than operation in the acutely ischemic group; that is, among those patients treated from 0 to 14 days. Was there a temporal clustering favoring patients with acutely ischemic limbs at 24 to 48 hours and, if so, how did you exclude acute embolic events in this group?